REMARKS

Claims 15-35 and 43-47 stand rejected. Reconsideration is respectfully requested. Claims 1-21, 36-42 and 48 are canceled. New claims 49-65 have been added. Accordingly, claims 22-35, 43-47 and 49-65 are currently pending.

New claims 49-65 reflect the subject matter of previously-presented claims 22-35 and 43-47, but use the language "consisting essentially of". Support for "consisting essentially of" language in the context of the subject claims can be found in the specification's teachings regarding the advantages of storing a thermostable polymerase separately with a non-nucleic acid polyanion. For example, paragraph 0090 of the published application provides that:

> "In an alternate embodiment, the non-nucleic acid polyanion can be added directly to the concentrated stock solution of the thermostable polymerase *before addition of this pre-inhibited polymerase to the polynucleotide synthesis reaction.* The pre-deposition of *the polymerase in its storage buffer* loads the thermostable polymerase with the non-nucleic acid polyanion. This technical solution of the invention circumvents the necessity of a pre-incubation step with the polyanion during set-up of the reaction *prior to addition of the primers and the temple (sic) nucleic acid.*" (Emphases added).

Paragraph 0087 provides further details regarding the storage buffer, describing for example how a thermostable polymerase and non-nucleic acid polyanion may be "combined at ambient temperature in a reaction mixture containing 35-100 mM monovalent cations and at least 1.5 mM magnesium." Such teachings indicate which additional components would not materially change the characteristics of the invention of the subject claims. See MPEP 2111.03 (The transitional phrase 'consisting essentially of' limits the scope of a claim to the specified materials or steps 'and those that do not materially affect the basic and novel characteristic(s)' of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976)).

With respect to all amendments and new claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Withdrawn Rejections and Finality

Applicants acknowledge the withdrawal of the finality of the previous Office Action and thank the Examiner for same. Action at page 2. Applicants also acknowledge with thanks the withdrawal of prior claim rejections under 35 USC §§ 102(b) and 103(a) based on Schinazi et al., Antimicrobial Agents and Chemotherapy, 1989, vol. 33, no. 1, pp. 115-117 ("Schinazi") and based on Diringer et al., US Pat. 5,153,181 ("Diringer").

Applicants note that all the remaining rejections involve Asada et al (WO 00/14218), as evidenced by its counterpart U.S. Patent No. 6,673,578 ("Asada"), and address each of these below.

Rejection of Claims 15-21 under 35 USC §§ 102(b) and 103(a)

Allegedly in view of Asada, claims 15-19 remain rejected under 35 USC § 102(b) and claims 20-21 are rejected under 35 USC § 103(c). Action at pages 3-8. Cancellation of claims 15-21, however, renders these rejections moot. Applicants respectfully request acknowledgement of same.

Rejection of Claims 22-34 and 43-47 under 35 USC § 103(a)

Claims 22-34 and 43-47 are rejected as allegedly being obvious in view of Asada in combination with Qiagen News, Issue No. 1, 1999, cover and pages 13-14 ("Qiagen"). Action at pages 8-13. The Office contends that Asada's teachings are "compatible" with the claimed relative molar concentrations of non-nucleic acid polyanion to thermostable polymerase, asserting that Asada's goal was in fact "to inhibit (reversibly) the DNA polymerase" and arguing that discovery of optimum ranges by routine experimentation is not inventive. Action at pages 7-8 and 9. Accordingly, the Office maintains that the only difference between Asada and the invention of the subject claims is the storage of the polymerase with an acidic substance, motivation for which the Office allegedly finds in Asada's suggestion to combine "some of the components" and in Qiagen's combination of all components except primers and templates. Action at pages 10-12. Applicants respectfully traverse, as neither Asada nor Qiagen teach the use of non-nucleic acid polyanions to reversibly inhibit the thermostable polymerase as presently

claimed and, moreover, both references actually teach away from providing the polyanions in a storage buffer with the polymerase.

A. Neither Asada nor Qiagen teaches relative molar concentrations for reversible inhibition

Asada fails to teach the inclusion of non-nucleic acid polyanion relative to the thermostable polymerase to reversibly inhibit the polymerase, as required by the subject claims, for at least the following three reasons:

(i) Asada's reference to "holding the DNA polymerase on its molecule" cannot support a conclusion that Asada teaches reversible inhibition rather than enhancement

As noted in Applicants' previous response, Asada teaches using acidic substances only in amounts for enhancing DNA-synthesizing activity, and repeatedly specifies their enhancing properties (see, e.g., column 9, line 15; column 9, lines 34-35; column 10, lines 16-17; column 13, lines 10-12). Despite Asada's repeated teachings regarding enhancement, the Office instead contends that Asada's purpose was in fact "to inhibit (reversibly) the DNA polymerase." Action at page 7. For support of this rather contrary conclusion the Office points to the following teachings in Asada:

> "The acidic substance or a salt thereof as mentioned above efficiently allows to exhibit (sic) the DNA polymerase activity or to hold the enzyme, whereby the interaction between the DNA and the enzyme can be properly regulated." (column 13, lines 14-18); and
>
> "The action of the acidic substance is not particularly limited, and it is considered to be on the bases (sic) of *holding the DNA polymerase on its molecule*, thereby suppressing the nonspecific interaction of the DNA polymerase to a template DNA, and of providing an optimal amount of the DNA polymerase for the template DNA. In other words, the DNA synthesis reaction efficiently progresses by optimizing the interaction between the template DNA and the DNA polymerase, *the interaction increasing with the progress of the DNA synthesis reaction*." (column 10, lines 32-41) (Emphasis added).

From this terse and confusing language the Office arrives at the conclusion that "Asada's purpose *was* to inhibit (reversibly) the DNA polymerase." Action at page 7.

Applicants respectfully submit that such a conclusion cannot reasonably be drawn from the referenced teachings, particularly since Asada repeatedly and consistently teaches that its acidic substances will enhance the DNA-synthesizing activity of the polymerase, rather than

inhibit it as presently claimed. Nowhere does Asada mention inhibition, far less reversible inhibition at the temperatures used in PCR. Indeed, the Office appears to equate Asada's use of the phrase "*holding the DNA polymerase on its molecule*" with inhibition of polymerase activity, when the final clause of the referenced teaching clearly indicates that exactly the opposite effect is desired, *i.e.*, an increase in polymerase activity. Applicants respectfully submit that the Examiner's proposed interpretation is simply unsupportable in light of the teachings of Asada as a whole. ("A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984); MPEP 2141.02 IV).

Moreover, the Office's conclusion regarding reversible inhibition appears to be based on improper hindsight reasoning, in which certain ambiguous sentences plucked from an otherwise contrary reference are construed so as to "fit" the subject claims, regardless of how strained that interpretation is or what the rest of the reference clearly teaches. Indeed, the Office's conclusion clearly stems from the understanding that non-nucleic acid polyanions can reversibly inhibit polymerization at certain relative molar concentrations and at certain temperatures, knowledge which can only be gleaned from Applicants' disclosure. Applicants respectfully submit that such hindsight reconstruction is impermissible. ("Any judgment on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and *does not include knowledge gleaned only from applicant's disclosure*, such a reconstruction is proper." *In re McLaughlin* 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971); MPEP 2145 X.A).

In light of Asada's constant emphasis on enhancing DNA synthesis, a more reasonable interpretation of the phrase "*holding the DNA polymerase on its molecule*" would be that the acidic substances should enhance polymerization by stabilizing the interaction of the polymerase on its own template molecule, i.e., holding the DNA polymerase onto the DNA template molecule to be replicated. Further, this interpretation clarifies the rest of the cited language. Indeed, stabilization of the polymerase onto its intended template would, of course, suppress nonspecific interactions of the polymerase with other potential but unintended templates, which explains the phrase: "thereby suppressing the nonspecific interaction of the DNA polymerase to

a template DNA" (column 10, lines 35-37). Moreover, the enhanced stability of the DNA polymerase on its intended template, rather than other competing, unintended templates, would necessarily provide "an optimal amount of the DNA polymerase for the template DNA" (column 10, lines 37-38). The very next sentence confirms this interpretation: "In other words, the DNA synthesis reaction efficiently progresses by *optimizing the interaction* between the template DNA and the DNA polymerase, *the interaction increasing with the progress of the DNA synthesis reaction*" (column 10, lines 38-41) (emphasis added). Finally, such an interpretation is also consistent with the remaining sentence cited by the Office:

> "The acidic substance or a salt thereof as mentioned above efficiently allows to exhibit (sic) the DNA polymerase activity or to hold the enzyme, whereby the interaction between the DNA and the enzyme can be properly regulated." (Column 13, lines 14-18).

This sentence suggests again that the acidic substance (or salt thereof) helps regulate the interaction of the DNA polymerase with its DNA template by holding the enzyme onto its template and making its polymerase activity more efficient.

There is, however, no teaching or suggestion anywhere in Asada that their acidic substances can or should be employed to inhibit polymerase activity. As indicated above, Asada's reference to "holding the DNA polymerase on its molecule" actually further supports Asada's focus on enhancement rather than inhibition of activity. Applicants respectfully and earnestly request re-consideration of this interpretation, without reliance on Applicants' own teachings and in light of the entirety of Asada that clearly points to a completely different functionality for their acidic substances.

(ii) Asada's teaching to modify MW does not constitute a teaching to optimize molar ratios

Having improperly concluded that Asada teaches reversible inhibition, the Office then extrapolates that Asada's suggestion to modify molecular weights of its acidic substances would be "compatible with the claimed molecular weights." Action at pages 7 and 9. In doing so, the Office relies on the tenet that it is not inventive to discover optimum ranges by routine experimentation. Action at pages 8 and 9.

Applicants respectfully traverse, as firstly, the premise on which this extrapolation lies is incorrect; and secondly, the extrapolation itself is scientifically unsound. First, as discussed in detail above, Asada repeatedly teaches that its acidic substances enhance DNA-synthesizing

activity and the point citations referenced by the Examiner simply do not support a contrary conclusion that the substances could or should cause reversible inhibition. Moreover, the tenet regarding the obviousness of discovering optimum ranges only applies where the prior art already teaches the result for which the variable is being optimized. ("A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a *recognized result*, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation." *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) (emphasis added); MPEP 2144.05(B)(II)). Asada does not contemplate, let alone teach, that its acidic substances could or should reversibly inhibit polymerase activity at any molar concentration relative to the thermostable polymerase. Accordingly, Applicants' teaching of compositions including non-nucleic acid polyanions that do reversibly inhibit polymerase activity cannot be deemed obvious nor routine.

Secondly, modifying the molecular weight of a substance is not "compatible" with optimizing its relative molar concentration. Asada discusses modifying the *molecular weight* of the acidic substance, but in doing so says nothing about varying its *molar concentration* relative to that of polymerase. Applicants respectfully point out that adjustments in molecular weight are not tantamount to optimizing relative molar concentrations. The relative molar concentration involves a ratio of the number of moles (or molecules) of acidic substance to the number of moles (or molecules) of polymerase, whereas the molecular weight of the acidic substance is merely a measure of the size of one of its molecules. Accordingly, modifying the molecular weight of a molecule of acidic substance, as taught in Asada, does not amount to varying the number of molecules of acidic substance used relative to the number of molecules of polymerase. Indeed, the lack of any clear teaching in Asada regarding optimizing relative molar concentrations further supports Applicants' conclusion that Asada's acidic substances were being used for a completely different functionality.

Qiagen, as noted in Applicants' previous response, does nothing to remedy this failing in Asada. Qiagen describes a master mix involving a modified thermostable polymerase, but provides no suggestion whatsoever to adjust relative amounts of the components used in Asada to achieve a result different from that taught in Asasda. A *prima facie* case for obviousness requires that the cited references teach every limitation of the claimed invention, but neither

Qiagen nor Asada can provide the molar ratio limitation. Lacking this limitation, neither Asada alone nor in combination with Qiagen can render the claimed invention obvious.

B. Both Asada and Qiagen teach away from providing the polyanions with the polymerase in the absence of template and/or primers

The Office contends that the only difference between Asada and the subject claims is the storage of the polymerase with an acidic substance. Action at pages 10-11. The Office then points to Asada as providing the motivation to combine "some of the components" and also to Qiagen as allegedly providing motivation to combine all components except primers and templates. Action at pages 11-12.

Applicants respectfully traverse since neither Asasa nor Qiagen can provide the motivation to include non-nucleic acid polyanions with polymerase in a storage buffer, in the absence of a template and/or primer, as both references teach away from making such a combination. Indeed, motivation to store the non-nucleic acid polyanions with polymerase only comes from a clear understanding of their ability to effect reversible inhibition, an understanding that is found solely in the instant application and thus cannot properly be used in deriving motivation. ("Any judgment on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and *does not include knowledge gleaned only from applicant's disclosure*, such a reconstruction is proper." *In re McLaughlin* 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971) (emphasis added); MPEP 2145 X.A). In contrast, Applicants respectfully submit that the combined teachings of Asada and Qiagen actually provides motivation to avoid adding Asada's acidic substances to polymerase in the absence of template and/or primer.

Asada makes only a passing reference to the possibility of combining "some of the components" (column 13, lines 34-39), and focuses exclusively on enhancing polymerase activity by the inclusion of acidic substances. Accordingly, one would expect the acidic substances to exhibit their function only in the context of polymerization, that is, only in the presence of template, primers, nucleotides, and other components needed for polymerization. Indeed, a skilled artisan would be motivated to add a polymerization-enhancing substance only to a reaction mixture, not to a stock solution lacking a template nucleic acid and/or its primer, as required by the subject claims.

Moreover, as discussed above, a reasonable interpretation of the mode of action of Asada's acidic substances involves helping to hold the polymerase onto its template. As such, Asada's acidic substances would not be expected to exhibit their sole function, enhancing polymerization by stabilizing the polymerase on its template, in the absence of any template, thus again teaching away from the subject claims. Accordingly, in light of Asada's teachings and in particular their proposed mode of action, one of skill in the art would understand that Asada's acidic substances only work in the presence of polymerization components, and thus would not be motivated to provide the acidic substances with polymerase in a stock solution that lacks templates and/or primers.

Qiagen does nothing to reverse this understanding and, in fact, further teaches away from adding Asada's acidic substances to polymerase outside the context of a polymerization reaction. Qiagen discusses the advantages of postponing initiation of polymerization by using a master mix of a modified polymerase that remains inactive at low temperatures. For example, the reference notes the convenience of room temperature setup and fewer pipetting steps afforded by the master mix in which polymerization is inhibited. Such teachings, Applicants respectfully submit, point away from providing the polymerase in a storage buffer with a polymerization-enhancer, as the problems supposedly addressed by Qiagen's master mix instead would be exacerbated. As Asada repeatedly touts the polymerization-enhancing function of its acidic substances, there is simply no basis for the skilled artisan to combine these teachings as suggested by the Examiner since doing so would be detrimental to the purpose sought by Qiagen.

It is axiomatic that a proposed modification cannot render the prior art unsatisfactory for its intended purpose. MPEP 2143.01 V ("If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)). As Asada touts the polymerization-enhancing function of its acidic substances and Qiagen contrarily teaches inhibiting the polymerization activity of a stored polymerase, the Office's proposed combination would be contrary to the express and intended purpose of Asada's acidic substances, on the one hand, and Qiagen's inhibited polymerase, on the other. Accordingly, there is no reasonable motivation that can be drawn from these references to make such a modification, and thus no *prima facie* case of obvious in view of the cited references.

Furthermore, new claims 49-65 are even further distinguished from the cited references. Claims 49-65 use "consisting essentially of" language. Such language further excludes additional components that would be needed for polymerization from the claimed stock solution containing the non-nucleic acid polyanion and polymerase. Since, as detailed above, the teachings of Asada combined with Qiagen would lead one of skill in the art to combine Asada's acidic substances with polymerase only in the context of a polymerization reaction, the new claims are undisputedly free of any obviousness issues in view of the cited art.

In sum, neither Asada nor Qiagen teach or suggest relative molar concentrations of non-nucleic acid polyanions that reversibly inhibit thermostable polymerase, while both references teach away from combining the polymerase with the non-nucleic acid polyanions in the absence of a template nucleic acid and/or its primer. For at least either one of these two reasons, Applicants earnestly and respectfully request reconsideration and withdrawal of the 103(a) rejections directed at claims 22-34 and 43-47.

Rejection of Claim 35 under 35 USC § 103(a)

Finally, claim 35 is rejected as allegedly being obvious in view of Asada in combination with Qiagen and further in view of Tonoike et al., US Pat. 6,472,187 ("Tonoike"). Action at pages 13-15. While acknowledging that neither Asada nor Qiagen teaches the reverse transcriptases of claim 35, the Office points to Tonoike as providing the missing element, in that Tonoike allegedly teaches RNA amplification using AMV reverse transcriptase. Action at page 14.

Applicants respectfully traverse based on the reasons provided above. That is, neither Asada nor Qiagen teach or suggest providing non-nucleic acid polyanions at a molar concentration relative to the themostable polymerase that reversibly inhibit the polymerase, as required by claim 22 from which claim 35 depends. Further, both Asada and Qiagen teach away from combining the non-nucleic acid polyanions with polymerase in the absence of a template nucleic acid and/or its primer, again as required by claim 22 from which claim 35 depends.

Tonoike does nothing to remedy either of these deficiencies. Tonoike pertains to a method for amplifying RNA directly from a biological sample using a reaction solution having a

polyamine, a sulfated polysaccharide and/or an elevated pH (see, e.g., column 5, lines 60-64). However, nothing in Tonoike addresses the issues of varying molar concentrations of non-nucleic acid polyanions relative to a thermostable polymerase to achieve reversible inhibition of the polymerase; nor including the non-nucleic acid polyanions in a storage buffer with the polymerase but without template and/or primers. As Asada in combination with Qiagen fails to provide the molar ratio limitation of the subject claims, and both teach away from excluding template and/or primer, as required in the claims, the combination of Tonoike with Asada and Qiagen still cannot render claim 35 obvious.

Accordingly, Applicants respectfully and earnestly request reconsideration and withdrawal of the 103(a) rejection directed at claim 35.

CONCLUSION

Applicants respectfully submit that the invention as presently claimed is both novel and nonobvious in view of the art references cited against this application. Applicants thus respectfully request entry of these amendments and earnestly and respectfully request timely allowance of pending claims 22-35, 43-47 and 49-72.

If a telephone call would help expedite any aspect of the prosecution of the instant application, Applicants encourage the Examiner to contact the undersigned by telephone at (415) 318-1200 or by fax at (415) 318-1300.

Respectfully submitted,
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